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PATENT

AMENDMENTS TO THE CLAIMS

Applicant acknowledges the following Examiner's Amendments to the present application:

Listing of Claims

1. (Previously withdrawn) A method of causing cardiomyocyte growth and/or differentiation, the method comprising exposing a cardiomyocyte to neuregulin (NRG) thereby activating the MAP kinase pathway in the cardiomyocyte and causing growth and/or differentiation of the cardiomyocyte.

2. (Canceled)

3. (Previously withdrawn) The method according to claim 1 wherein neuregulin is provided directly to the cardiac cell or provided indirectly by causing neuregulin to be produced in other cells by inducing expression of the gene (s) involved in neuregulin production.

4. (Previously withdrawn) The method according to claim 1 wherein neuregulin production is in the cardiac muscle cell to which the method is directed in an autocrine manner or produced by some other cell and released in a paracrine manner.

5. (Previously withdrawn) The method according to claim 1 wherein function of a normal or diseased heart is improved by the treatment with neuregulin.

6. (Previously withdrawn) A method of identifying polypeptides or compounds which stimulate cardiac muscle cell differentiation, the method comprising contacting the cardiac muscle with a test polypeptide or compound in the presence of an inducer of cardiac muscle cell proliferation in the form of neuregulin, and measuring the development of cardiac muscle cell differentiation.

7. (Previously withdrawn) The method according to claim 6 wherein the differentiation of cardiac muscle cells is measured in cells exposed to neuregulin or other test polypeptides, or to a mixture of neuregulin with a test polypeptide.

8. (Previously withdrawn) The method according to claim 6 wherein differentiation of cardiac muscle cell is measured by a test selected from the group consisting of calculation of increases or decreases in DNA synthesis, analysis of the timecourse of phosphorylation of MAP kinases in cardiac muscle cells, evaluation of the expression of cell cycle inhibitor, p21CIP1, phenotypic organisation of contractile units, accumulation of contractile units, phenotypic alteration of cytoskeleton actin fibers, and phenotype of cell-cell adhesions.

9. (Previously withdrawn) The method according to claim 6 wherein cells are incubated with different concentrations of various peptides or compounds and the effect of the test peptide or compound in different concentrations on cardiac muscle cell differentiation is measured.

10. (Previously withdrawn) The method according to claim 6 wherein cells are incubated with IGF-1, with and without the test polypeptide or compound, and the ability of the test polypeptide or compound to inhibit IGF-1-mediated cardiac muscle cell DNA synthesis, assembly of sarcomeric structures and cell-cell adhesions are measured.

11. (Previously withdrawn) The method according to claim 6 wherein the cells are incubated with phenylephrine (PE) with and without the test polypeptide or compound, and the ability of the test polypeptide or compound to augment PE-mediated cardiac muscle cell differentiation is determined.

12. (Previously withdrawn) The method according to claim 6 wherein the test polypeptide stimulates cardiac muscle cell differentiation and stimulates the assembly of sarcomeres thus enhancing heart function by activating neuregulin-specific receptors ErbB2, ERbB3 and ErbB4.

13. (Previously withdrawn) A method of identifying polypeptides or compounds which inhibit neuregulin stimulation of ventricular muscle cell differentiation, the method comprising contacting the ventricular muscle cell with the test polypeptide or compound in the presence neuregulin and measuring any inhibition of neuregulin stimulation of the ventricular muscle cell.

14. (Previously withdrawn) The method according to claim 13 wherein the compound inhibits neuregulin stimulation of ventricular muscle cell differentiation by blocking, suppressing, reversing, or antagonising the action of neuregulin.

15. (Previously withdrawn) The method according to claim 14 wherein the measurement is by detecting DNA synthesis of ventricular muscle cells.

16-17. (Canceled)

18. (Previously withdrawn) A method of preventing or lowering the incidence of heart disease in a mammal, the method comprising preventing or lowering the interference or effects of polypeptides or compounds on the action of neuregulin and its receptors, ErbBs, that produce heart failure.

19. (Previously withdrawn) Use of therapeutic agent which mimics the effects of neuregulin to treat or prevent PE, or IGF-1-mediated cardiac muscle cell dysfunction.

20. (Previously withdrawn) A method of determining predisposition to heart disease or heart failure in a subject, the method comprising testing cardiac or related muscle cells of the subject for the ability to express and/or produce normal or adequate levels of neuregulin or its cognate ErbB receptors.

21. (Previously withdrawn) The method according to claim 20 wherein the inability to express and/or produce normal or adequate levels of neuregulin being indicative of predisposition to heart disease or heart failure.

22. (Previously withdrawn) Use of neuregulin, neuregulin polypeptide, neuregulin derivatives, or compounds which mimic the activities of neuregulins in the treatment or management of heart disease and heart failure in a mammal.

23. (Previously withdrawn) The use according to claim 22 wherein the concentration of neuregulin, neuregulin polypeptide, neuregulin derivatives, or compounds which mimic the activities of neuregulins is at least 10^{-8}M.

24. (Previously withdrawn) Use of neuregulin, neuregulin polypeptide, neuregulin derivatives, or compounds which mimic the activities of neuregulins in the manufacture of a medicament for the treatment or management of heart disease and heart failure.

25-27. (Canceled)

28. (Previously withdrawn) The method according to claim 3 wherein function of a normal or diseased heart is improved by the treatment with neuregulin.

29. (Previously withdrawn) The method according to claim 4 wherein function of a normal or diseased heart is improved by the treatment with neuregulin.

30. (Currently amended) A method of inducing remodeling of cardiac muscle cell sarcomeric and cytoskeleton structures or cell-cell adhesions, which method comprises contacting cardiac muscle cells with a neuregulin protein[[,]] consisting of an amino acid sequence set forth in SEQ ID NO:2, in [[an]] the amount sufficient to activate the MAP kinase pathway in said cardiac muscle cells and induce remodeling of said cardiac muscle cell sarcomeric and cytoskeleton structures or cell-cell adhesions.

31-36. (Canceled)

37. (Previously presented) The method of claim 30, wherein the neuregulin protein is used in an amount that is at least 10^{-8}M.

38. (Previously presented) The method of claim 30, wherein the cardiomyocyte or the cardiac muscle cells exist in a mammal.

39. (Previously presented) The method of claim 38, wherein the mammal is a human.

40. (Previously presented) The method of claim 39, wherein the human has or is suspected of having a heart failure.

41. (Currently amended) The method of claim 40, wherein the heart failure is a disease state selected from the group consisting of congestive heart failure, myocardial infarction, ~~tachyarrythmia~~ tachyarrhythmia, familial hypertrophic cardiomyopathy, ischaemic heart disease, idiopathic dilated cardiomyopathy and myocarditis.

42. (Previously presented) The method of claim 40, wherein the heart failure is in the form of ischaemic, congenital, rheumatic, or idiopathic.

43. (Previously presented) The method of claim 40, wherein the heart failure results from disassociation of cardiac muscle cell-cell adhesion and/or the disarray of sarcomeric structures in the mammal.

44. (Previously presented) The method of claim 38, wherein the neuregulin protein is administered with a pharmaceutically acceptable carrier or excipient.

45. (Previously presented) The method of claim 30, wherein the contact of the cardiac muscle cells with the neuregulin protein decreases DNA synthesis in the cardiac muscle cells.

46. (Previously presented) The method of claim 30, wherein the contact of the cardiac muscle cells with the neuregulin protein results in sustained activation of the MAP kinase pathway in the cardiac muscle cells.

47. (Previously presented) The method of claim 38, wherein the neuregulin protein is administered orally, using a sustained-release system or via injection or infusion.

48. (Previously presented) The method of claim 47, wherein the injection or infusion is selected from the group consisting of intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial and intralesional injection or infusion.

49. (Previously presented) The method of claim 30, which further comprises contacting the cardiac muscle cells with an effective amount of an agent which causes cardiac hypertrophy or congestive heart failure.

50. (Previously presented) The method of claim 49, wherein the agent which causes cardiac hypertrophy or congestive heart failure is fludrocortisone acetate or herceptin.

51. (Previously presented) The method of claim 30, which further comprises contacting the cardiac muscle cells with an effective amount of an agent that acts to suppress a hypertrophy induction pathway different from the pathway suppressed by the neuregulin.

52. (Previously presented) The method of claim 51, wherein the agent that acts to suppress a hypertrophy induction pathway different from the pathway suppressed by the neuregulin is selected from the group consisting of a cardiotrophic inhibitor, an angiotensin-converting enzyme (ACE) inhibitor, a human growth hormone, an IGF-I, an anti-hypertrophic, myocardiotrophic factor, an anti-arrhythmic factor and an inotropic factor.

53. (Previously presented) The method of claim 30, which further comprises contacting the cardiac muscle cells with an effective amount of an angiotensin-converting enzyme (ACE) inhibitor.

54. (Previously presented) The method of claim 53, wherein the ACE inhibitor is selected from the group consisting of quinapril, ramipril, captopril, benazepril, fosinopril, lisinopril, enalapril and lisinopril.

55. (Previously presented) The method of claim 30, which further comprises contacting the cardiac muscle cells with an effective amount of an agent for treating hypertension.

56. (Previously presented) The method of claim 55, wherein the agent for treating hypertension is selected from the group consisting of an antibody to the endothelin receptor, a β-adrenoreceptor antagonist, an α_1-noreceptor antagonist, an anti-oxidant, a β-blocker and a growth hormone.

57. (Currently amended) A method for treating or delaying disassociation of cardiac muscle cell-cell adhesion and/or the disarray of sarcomeric structures in a mammal, which method comprises administering to a mammal, to which such treatment or delay is needed or desirable, a neuregulin protein [[,]] consisting of [[an]] the amino acid sequence set forth in SEQ ID NO:2, in an amount sufficient to activate the MAP kinase pathway in said mammal, whereby said disassociation of cardiac muscle cell-cell adhesion and/or the disarray of sarcomeric structures is treated or delayed in said mammal.

58. (Canceled)

59. (Previously presented) The method of claim 57, wherein the mammal is a human.

60. (Previously presented) The method of claim 59, wherein the human has or is suspected of having a heart failure.

61. (Currently amended) The method of claim 60, wherein the heart failure is a disease state selected from the group consisting of congestive heart failure, myocardial infarction, ~~tachyarrythmia~~ tachyarrhythmia, familial hypertrophic cardiomyopathy, ischaemic heart disease, idiopathic dilated cardiomyopathy and myocarditis.

62. (Previously presented) The method of claim 60, wherein the heart failure is in the form of ischaemic, congenital, rheumatic, or idiopathic.

63. (Previously presented) The method of claim 57, wherein administration of the neuregulin protein decreases DNA synthesis in the cardiac muscle cells of the mammal.

64. (Previously presented) The method of claim 57, wherein administration of the neuregulin protein results in sustained activation of the MAP kinase pathway in the cardiac muscle cells of the mammal.